Beta-lactam Allergies: Misadventures of Misreporting

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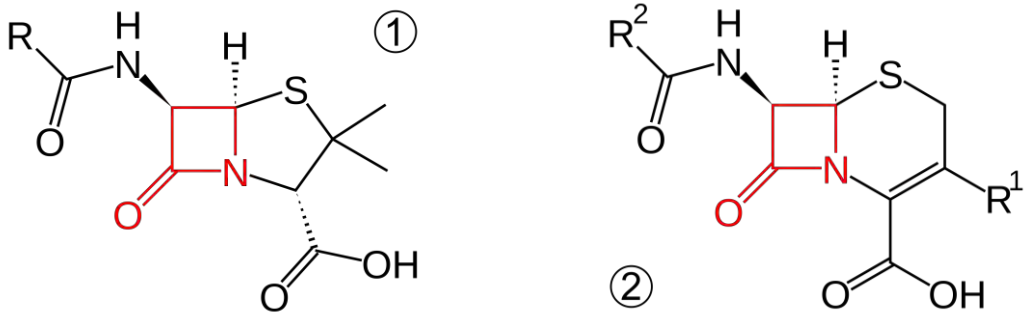
Disclosures

- Nothing to disclose

Objectives

- Explain the public health concerns of misreported allergies
- Distinguish between different types of drug reactions
- Systematically evaluate a reported drug allergy
  - Specifically, an allergy to penicillin
- Develop a plan for the management of a patient with a reported penicillin allergy



Examples:

Penicillins, aminopenicillins, cephalosporins, carbapenems, monobactams, and *beta-lactamase inhibitors*

Broad class of antibiotics that includes penicillins
Characterized by beta-lactam ring

Drugs of choice for several indications!

REPORTED BETA-LACTAM ALLERGIES ARE A MAJOR PUBLIC HEALTH ISSUE

Beta-Lactam Allergies: A major public health issue!

- Penicillin allergy first documented in 1946
  - Most common beta-lactam and drug class allergy
  - Reported by **up to 10% of individuals** in USA
- Prevalence of true *IgE-mediated* allergy
  - **Only 10-15% of patients with a reported penicillin allergy**
  - Most common between ages 20-49
  - Anaphylaxis in 1 to 2 per 10,000 treated patients

Ann Allergy Asthma Immunol. 2010;105(4):259-273.
Clin Exp Allergy. 2015;45(2):300-27.
Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
Curr Allergy Asthma Rep. 2014;14(11):476.

But **why** is this a major public health issue?

- **Preferred beta-lactam therapy is avoided in >50% of patients, even when a non-severe prior reaction is reported**
  - Alternatives often less effective, more costly, and more toxic

- Beta-lactams (nafcillin/cefazolin) superior to vancomycin for methicillin-susceptible *S. aureus* (MSSA) bacteremia
  - Retrospective cohort, 267 patients
  - Mortality: Adjusted HR of 0.21 (95% CI: 0.09-0.47)

Clin Infect Dis 2016;63:904-10.
BMC Infect Dis. 2011 Oct 19;11:279.

A MAJOR Public Health Issue.

Study	Objective	Patients	Results
Jeffres et al Retrospective Multicenter	Clinical failure with beta-lactam (BL) or non-beta-lactam (NBL) with BL allergy in G- bacilli bloodstream infections	433 in BL group 119 in NBL group	⇧ **Clinical failure in NBL** (38.7% vs 27.4%, p=0.03) ⇧ **Length of stay in NBL** (30.9 vs 21.5 days, p=0.065) ⇩ **Appropriate empiric abx** (74.8% vs 91.7%, p<0.001) Overall Hypersensitivity rate: 2.9%
Macy et al Retrospective Matched cohort study	**Outcomes with and without penicillin "allergy" at admission**	Matched 51,582 hospitalizations with penicillin allergy	⇧ **Length of stay:** 0.59 days (95% CI, 0.47-0.71) ⇧ **C. difficile:** 23.4% (95% CI, 15.6% to 31.7%) ⇧ **MRSA:** 14.1% (95% CI, 7.1% to 21.6%) ⇧ **VRE:** 30.1% (95% CI, 12.5% to 50.4%)

Antibiotics and Risk of Community-acquired *C. diff*

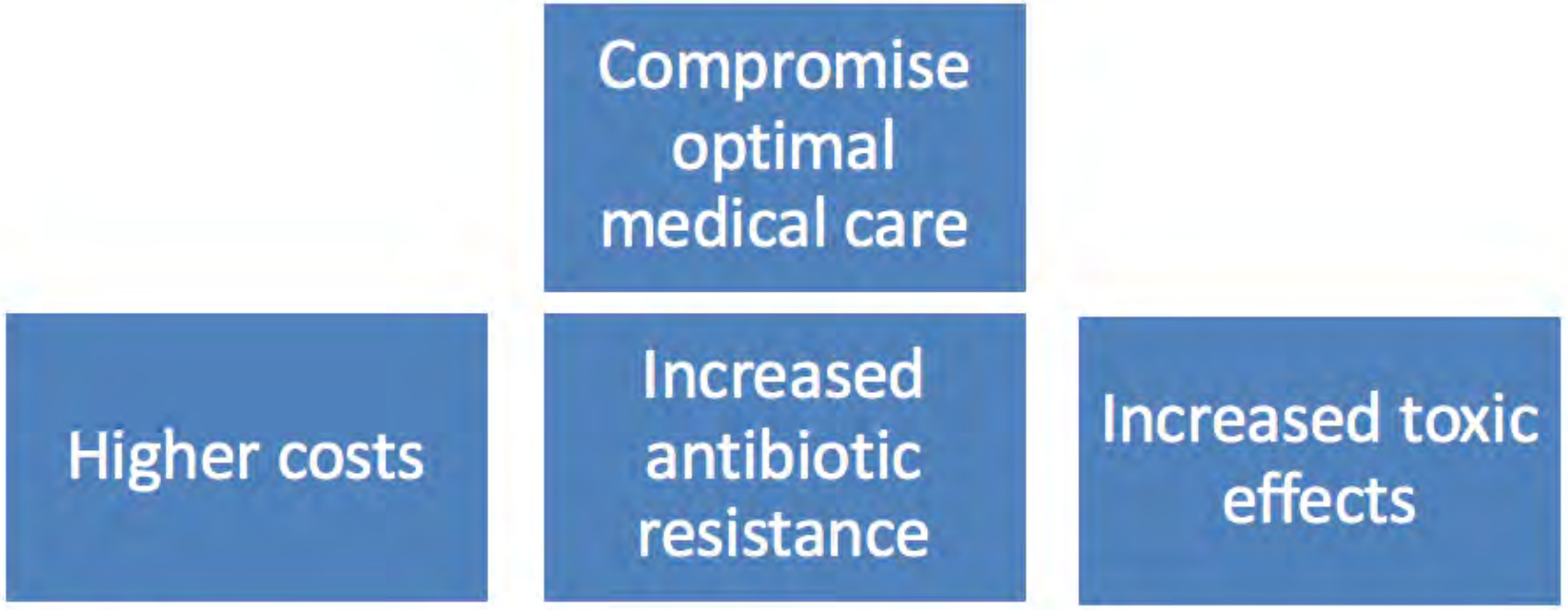
Class	Odds Ratio vs. no antibiotics	95% CI
Clindamycin	**16.80**	7.48 to 37.76
Fluoroquinolones (e.g. ciprofloxacin, levofloxacin)	**5.50**	4.26 to 7.11
Cephalosporins, monobactams (e.g. aztreonam), and **carbapenems** (e.g. meropenem)	**5.68**	2.12 to 15.23
Penicillins	2.71	1.75 to 4.21
Macrolides (e.g. azithromycin, erythromycin)	2.65	1.92 to 3.64
Sulfonamides and trimethoprim (e.g. SMX/TMP)	1.81	1.34 to 2.43
Tetracyclines (e.g. doxycycline)	0.92	0.61 to 1.40
ANY ANTIBIOTIC	**3.55**	**2.56 to 4.94**

Highest risk is amongst drug classes commonly used in patients with a reported penicillin allergy

Antimicrob Agents Chemother. 2013;57(5):2326-32.

Key Points

- **Up to 90% of reported penicillin allergies are not true allergies**
- **Beta lactams often avoided in the presence of an allergy**
- **Unverified beta-lactam allergies represent a major public health issue**



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Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
J Allergy Clin Immunol. 2016;137(4):1148-53.

Why do we care? (and what can we do?)

- **We need to be able to distinguish to optimally treat patients**
- Clarification of beta-lactam allergies
  - Detailed patient interview
  - Cross-reactivity concerns
- Treating a patient with a reported penicillin allergy
  - Penicillin skin testing?
  - Graded drug challenge vs. desensitization

Types of Drug Reaction

Type A

- 85-90% of all adverse effects
- **Predictable from pharmacologic properties of the drug**
- Ex) Diarrhea from antibiotics, hypoglycemia from insulin

Type B

- 10-15% of drug reactions
- **Hypersensitivity reactions**
- Signs/symptoms differ from the pharmacologic action of drugs and **cannot be predicted**

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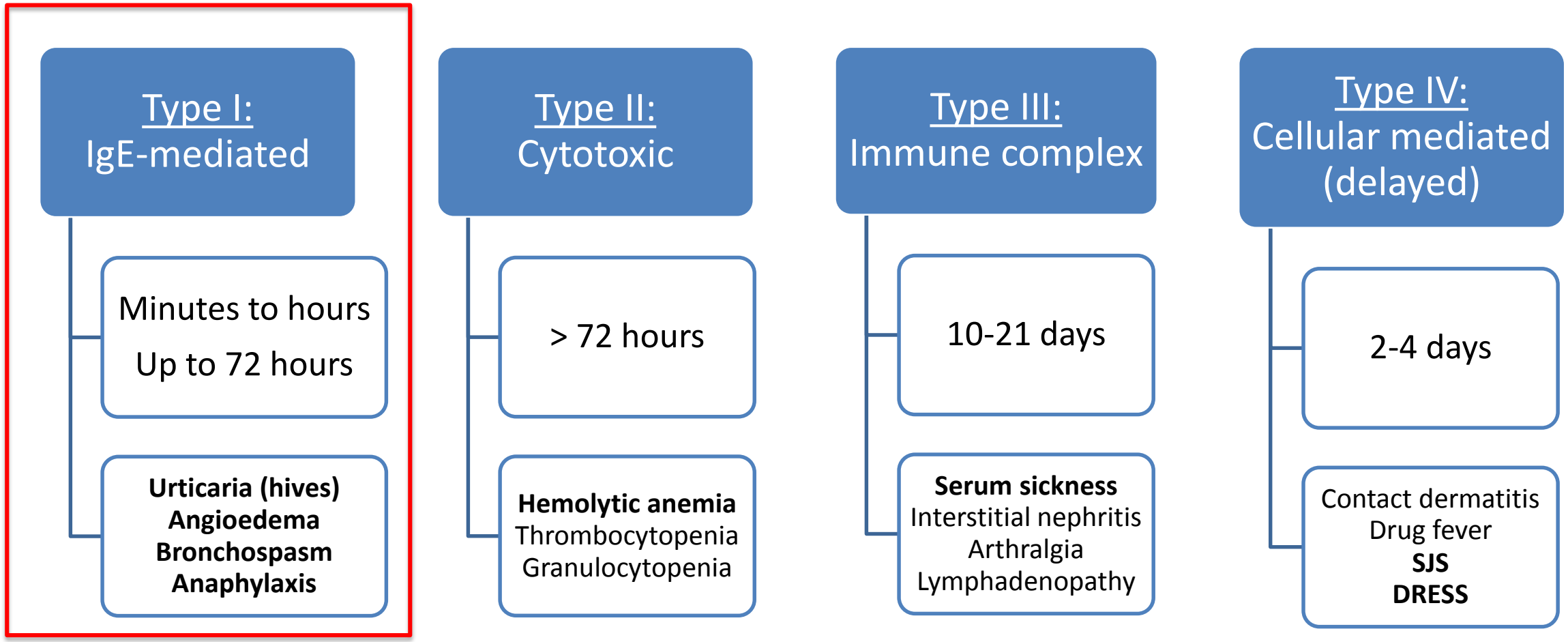
Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

Hypersensitivity (Type B) Reactions



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Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

Why are there so many ***reported*** allergies?

- Type A reactions **misreported** as an allergy
- Penicillins **can cause all 4** Type B drug reactions
- Childhood allergies:
  - Rashes and viral infection
  - Unclear history
- Family history
  - No predictable pattern to inheritance

Ann Allergy Asthma Immunol. 2010;105(4):259-273.
Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

Key Points

- Penicillins can cause several different types of drug reactions
- **Up to 90%** of drug reactions are **non-allergic** in nature
  - Often misreported as allergies!
- Type I hypersensitivity reactions are **immediate** and are mediated by drug-specific IgE antibodies
  - Distinct from other types of reactions

Why do we care? (and **what can we do?**)

- We need to be able to distinguish to optimally treat patients
- **Clarification of beta-lactam allergies**
  - **Detailed patient interview**
  - **Cross-reactivity concerns**
- Treating a patient with a reported penicillin allergy
  - Penicillin skin testing?
  - Graded drug challenge vs. desensitization?

Obtaining a Detailed History

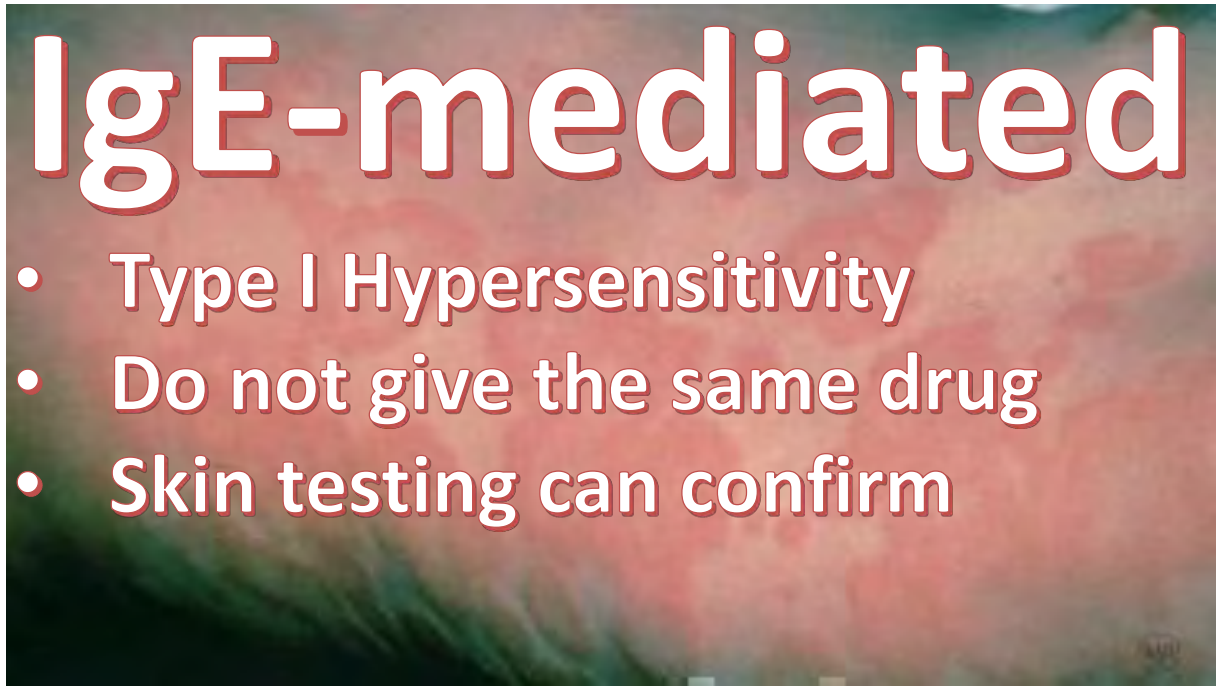
- **What penicillin** did you take?
- What **symptoms** did you experience?
  - **How long into therapy** did you experience these symptoms?
  - **How long ago** did this reaction happen?
  - What **other medications** were you taking when you had this reaction?
- Have you taken a **penicillin** since this reaction?
  - Have you ever taken a **cephalosporin**?

WHAT PENICILLIN DID YOU TAKE?

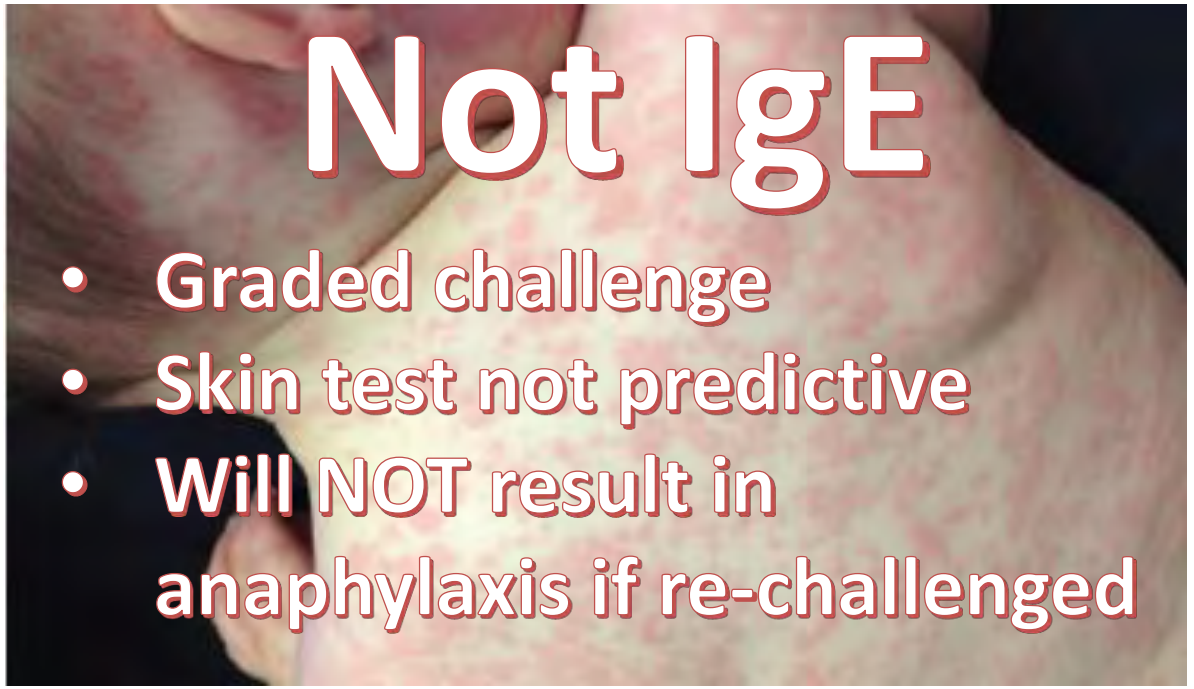
WHAT SYMPTOMS DID YOU EXPERIENCE?

- Wheezing, throat or mouth swelling, hives/rash?
- Did you have to go to the hospital or emergency room?
- If a rash occurred what did it look like?

Hives (Urticaria) vs. Rash



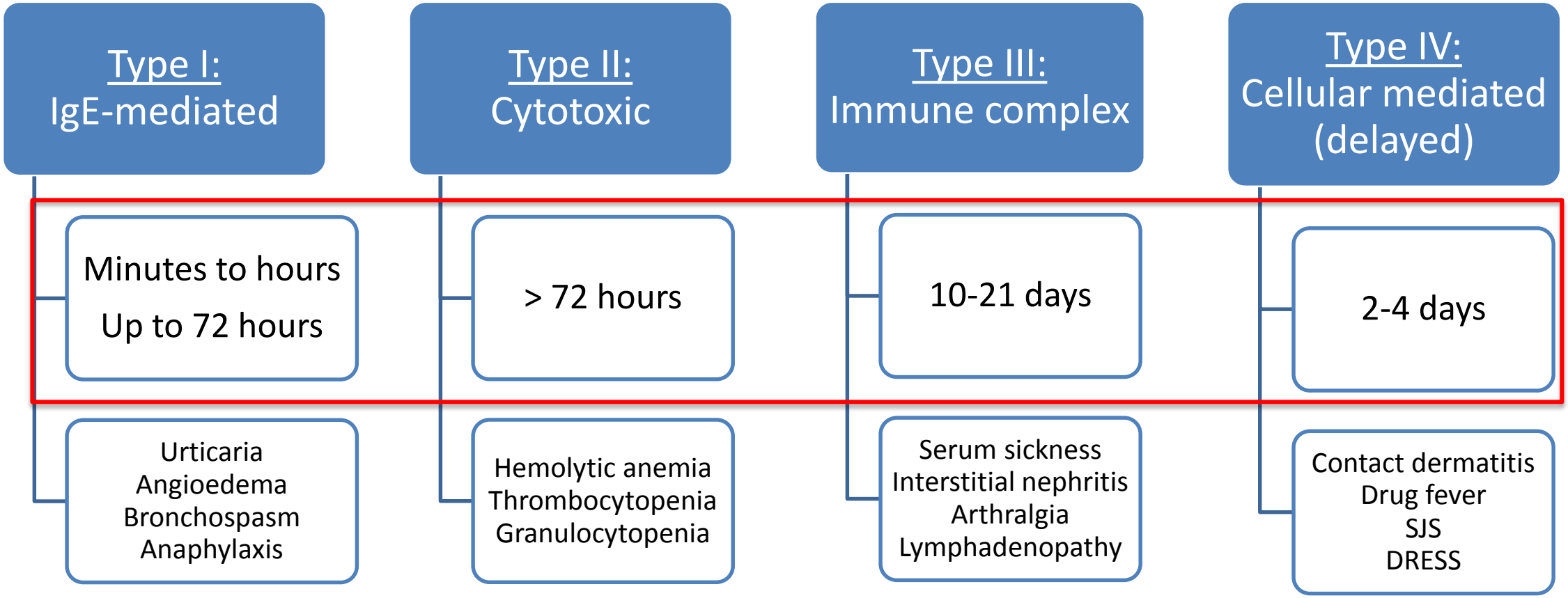
https://www.aad.org/public/diseases/itchy-skin/hives



http://www.pediatricsconsultant360.com/article/maculopapular-rash-after-otitis-media-10-month-old

HOW LONG INTO THERAPY DID THIS OCCUR?

Hypersensitivity (Type B) Reactions



Ann Allergy Asthma Immunol. 2010;105(4):259-273.
Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

HOW LONG AGO DID THIS HAPPEN?

Childhood allergies

- Viral illness can present with rash
- Higher risk of Type IV reaction with viral infections and exacerbation of autoimmune disease
- Children with EBV receiving aminopenicillins have demonstrated non-reproducible rashes
  - 90% of patients receiving ampicillin with EBV demonstrated non-pruritic morbilliform rash

J Allergy Clin Immunol 2011;127:218-22.
Pediatrics. 1967 Nov;40(5):910-1.

Is it safe now?

Patients may “outgrow” allergy

- Even with a well-documented allergy, hypersensitivity may not persist over time due to **loss of anti-PCN IgE antibodies**
  - 10 years: ~50% will lose allergy
  - 15 years: ~75% will lose allergy

HAVE YOU TAKEN PENICILLIN SINCE THEN?

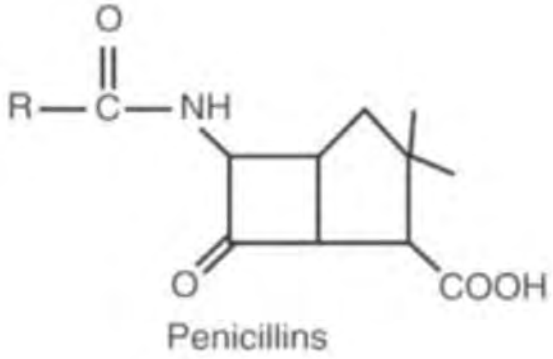
WHAT HAPPENED?

- Or other penicillins? (amoxicillin, nafcillin, etc.)

WHAT ABOUT A CEPHALOSPORIN?

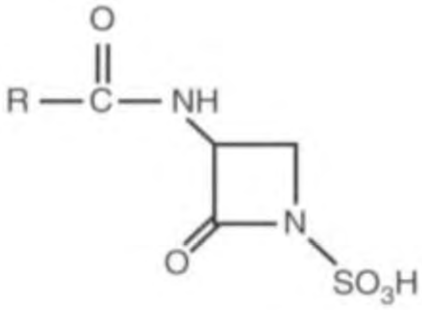
WHAT HAPPENED?

- Use both trade names and generic names
- Ask about IV and PO antibiotics
- Other beta-lactams: carbapenems, monobactams (aztreonam), etc.



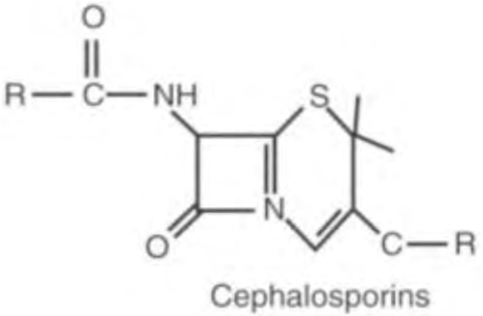
Penicillins

Cross-reactivity: Cephalosporins

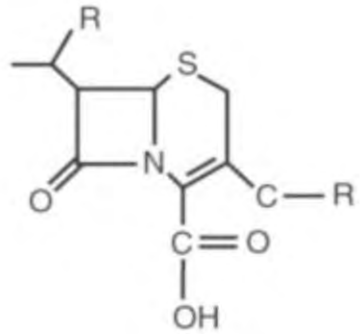


Monobactams

- Early reports: Up to 41%!! (Mostly in the 10-20% range)
  - Until 1982, cephalosporins were contaminated with penicillin
  - Non-allergic ADEs reported as drug allergies (Type A)
  - Cephalothin was commonly used
- Multiple drug allergy syndrome
- 1-3% incidence of reaction **independent** of penicillin allergy



Cephalosporins

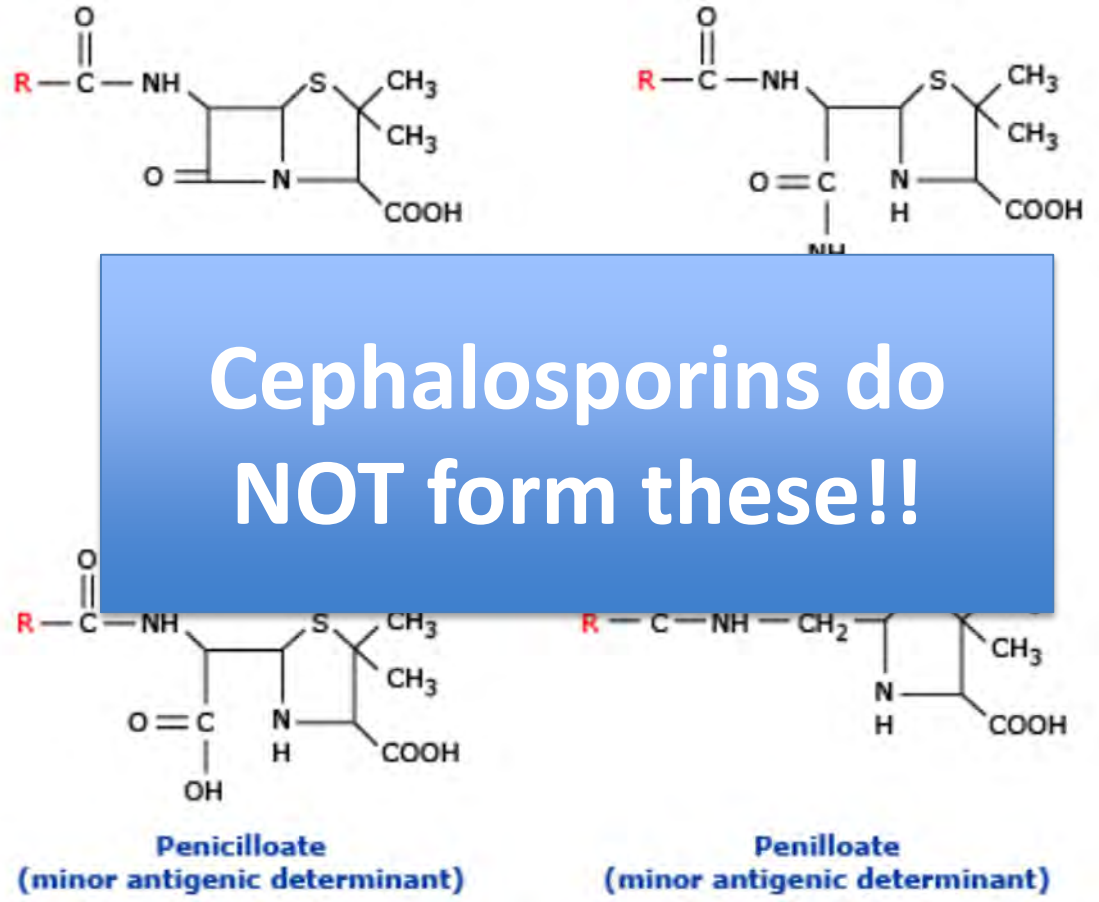


Carbapenems

J Am Pharm Assoc. 2008;48(4):530-540.
J Emerg Med 2012;42:612-620.
Am J Med. 2006;119(4);354.e11.
Ann Allerg Asth Immun 1995;74:167-170.

Determinants of IgE-mediated Penicillin Allergy

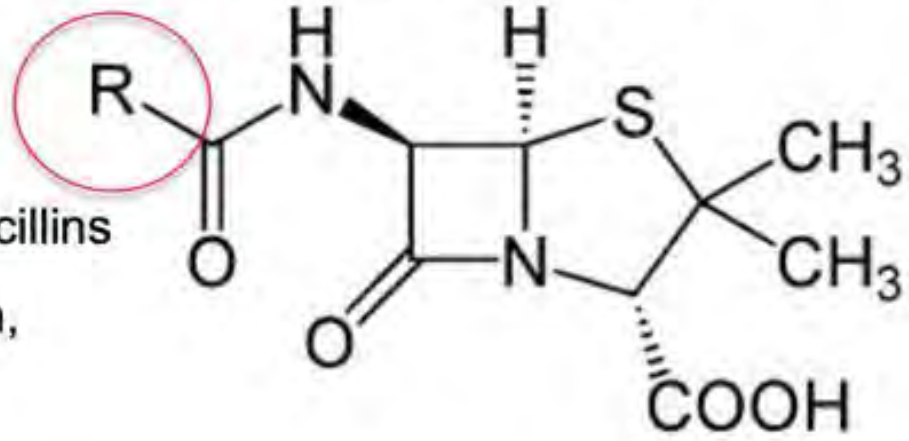
- Penicillin immunologically inert
  - Formation of hapten is necessary
- Converted to reactive intermediates under physiologic conditions
  - Ring opening
  - Degradation in the GI tract
- Major determinant responsible for > 75% of reactions



Pharmacother 2013;33:856-67.
NEJM 2006;354:601-609

Side Chain Theory

Penicillin Core Structure

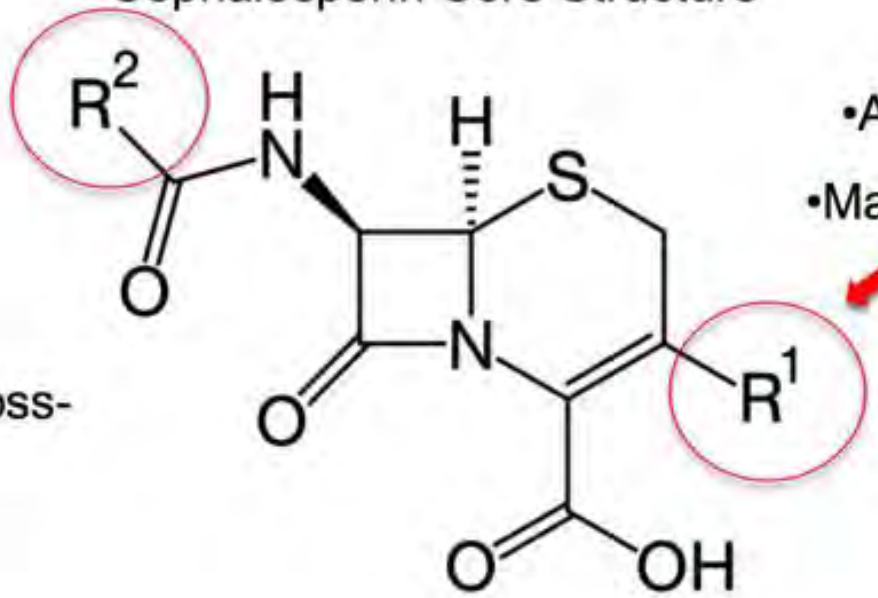


6-Position:

- Differentiates all penicillins

(Ampicillin, Piperacillin, Oxacillin, etc.)

Cephalosporin Core Structure



7-Position:

- Alters microbiologic properties
- Determines penicillin cross-reactivity

3-Position:

- Alters PK properties
- May determine cross-reactivity among cephalosporins

J Am Pharm Assoc. 2008;48(4):530-540.
http://en.wikipedia.org/wiki/Penicillin
http://en.wikipedia.org/wiki/Cephalosporin

Side-Chain Similarities

- Similarities between the penicillin 6-position and cephalosporin 7-position may cause cross-reactivity

Patient Allergic To:	Avoid:
Penicillin	Cephalothin (1st) Cephalodrine (1st) **Cefoxitin (2nd)**
Amoxicillin	**Cefadroxil (1st)** **Cefprozim (2nd)**
Ampicillin	**Cephalexin (1st)** Cephadrine Cephalolycin **Cefaclor (2nd)**
Ceftazidime	**Aztreonam**

J Fam Pract 2006;55:106-112.
Infect Dis 2007;57:13S-18S.
J Emerg Med 2012;42:612-620.

No cross-reactivity with cephalosporins in patients with penicillin allergy

- **Objective:** Evaluation of cross-reactivity between penicillin and cephalosporins
- **Methods:** Observational, retrospective study
- **Results:** 22 patients evaluated (10 cutaneous, 12 cardio/resp rxn)
  - Allergy – 7 Amoxicillin, 14 Amox/Clav, 1 Penicillin
  - Ceftriaxone and ceftazidime skin tests negative for all patients
- **Conclusions:** Certain cephalosporins are safe for patients with penicillin allergy (third and fourth generation)

J Investig Allergol Clin Immunol. 2015;25(3):216-7.

So is there cephalosporin cross-reactivity?

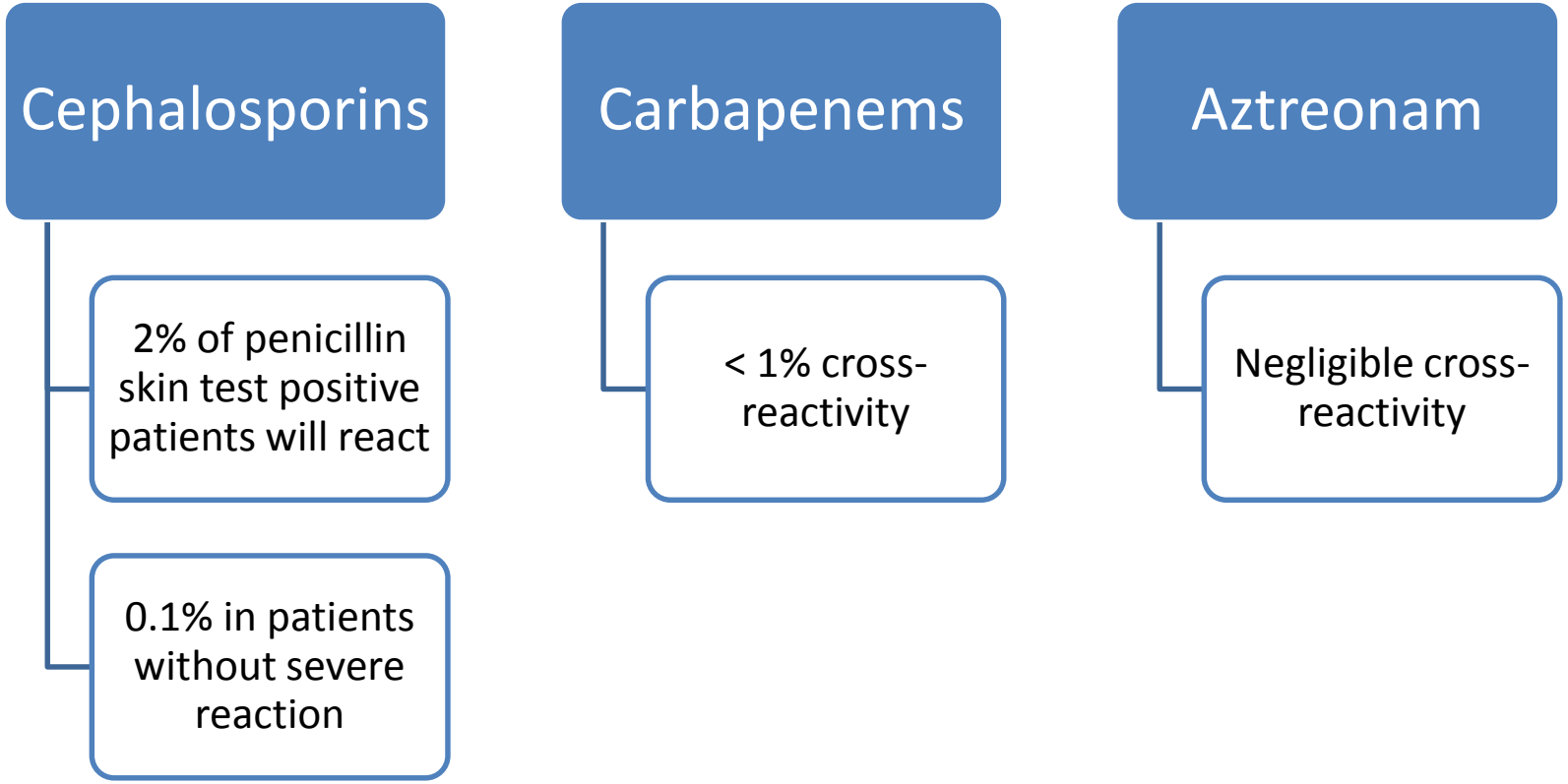
- True incidence: 0-5%
  - Similar side chains: higher risk
  - Minimal cross-reactivity with 2nd, 3rd, 4th generations

Other Beta-lactam Cross-reactivity

- Carbapenems (e.g. meropenem, ertapenem, imipenem)
  - Early reports: 47.4%!!
    - Flawed design using imipenem-cilastatin skin test, no actual doses given
  - Recent prospective studies: <1% !!
- Monobactams (aztreonam)
  - Essentially 0% cross-reactivity
  - Shares a side chain with ceftazidime!

J Allerg Clin Immunol. 1988;82(2):213-7.
J Pharm Pract. 2014;27(6):530-44.

Cross-reactivity: Summary



Ann Allergy Asthma Immunol. 2010;105(4):259-273.
Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
Curr Allergy Asthma Rep. 2016 Mar;16(3):24.

WHAT OTHER MEDICATIONS WERE YOU TAKING?

Why do we care? (and **what can we do?**)

- We need to be able to distinguish to optimally treat patients
- Clarification of beta-lactam allergies
  - Detailed patient interview
  - Cross-reactivity concerns
- **Treating a patient with a reported penicillin allergy**
  - **Penicillin skin testing?**
  - **Graded drug challenge vs. desensitization**

Suspected Type I reaction

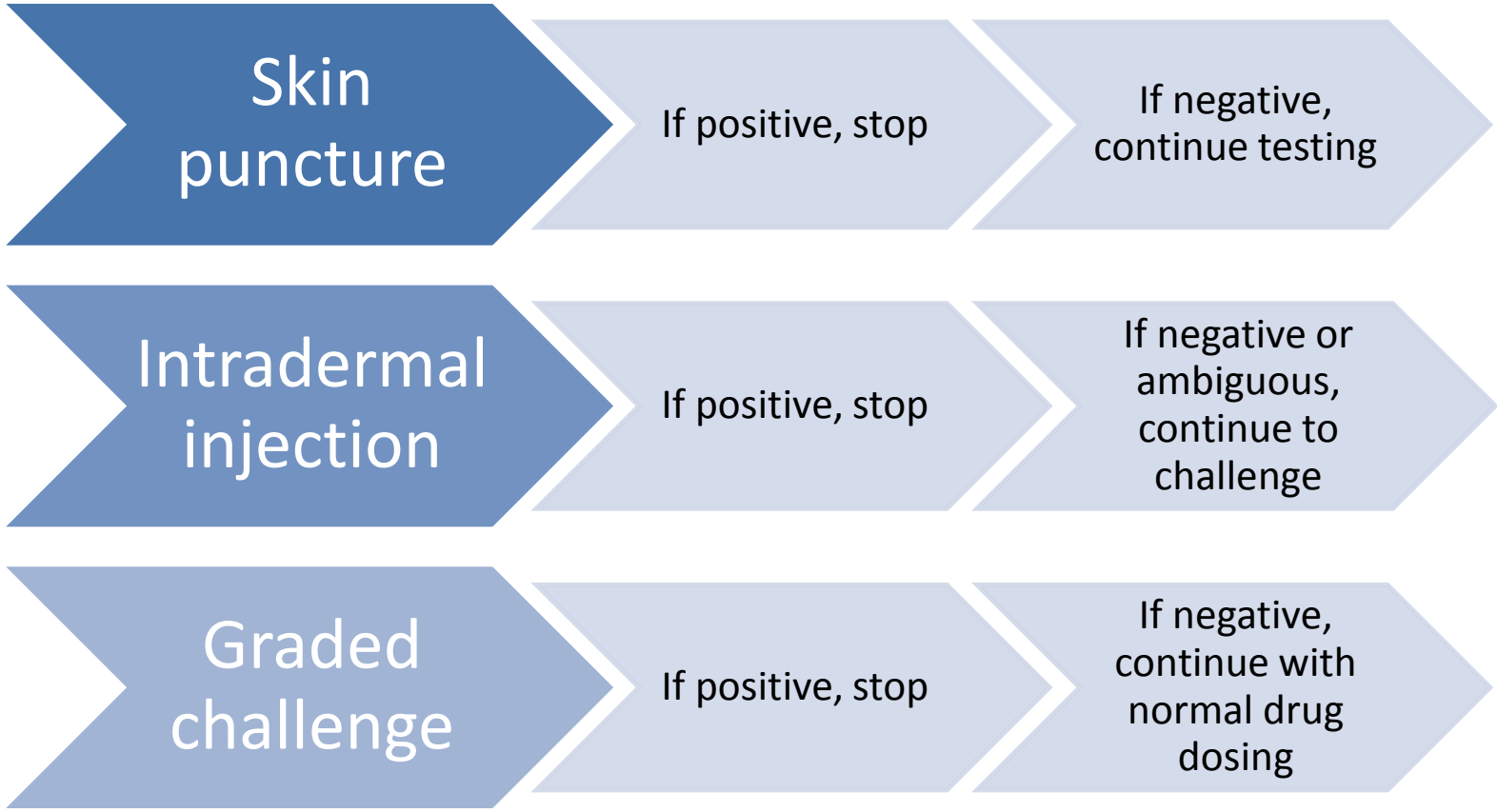
- ***Penicillin skin testing*** is diagnostic
- ***Desensitization*** or “induction of drug tolerance”
- Consider alternative antibiotics based on the history and severity of reaction
  - History of tolerating other beta-lactams?
  - 3rd, 4th generation cephalosporins, monobactams, and carbapenems
  - Be mindful of side chains

Penicillin Skin Test

- Evaluates IgE-mediated allergy
  - Not Types II-IV, Type A, or idiosyncratic
  - AVOID if history of SJS or TEN, extreme hypersensitivity
- Useful for ruling out allergy
  - Negative predictive value: 97-99%
  - Positive predictive value: 50%
- Can be done in an outpatient setting
- Now recommended in antimicrobial stewardship guidelines

Pharmacother 2013;33:856
Ann Allergy Asthma Immunol 2007:98:355.
Clin Infect Dis 2016;62:e51-77

Penicillin Skin Test



*Avoid H1-antihistamines and vasopressors for 48 hours before

Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
Pre-Pen ® [package insert]. 2009.

Penicillin Skin Test

https://penallergytest.com/procedure/

- Four substances:
  - Minor determinants: Penicillin G
  - Major determinant: Benzyl penicilloyl polylysine (Pre-Pen®)
  - Negative control: saline
  - Positive control: histamine

Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
Pre-Pen ® [package insert]. 2009.
Intensive Care Med. 2014;40:462

Negative Penicillin Skin Test

- <5% risk of reaction after penicillin administration
  - Negative predictive value for tolerance is 99%
- Cephalosporin administration with minimal concern for reaction
  - Regardless of severity
  - Consider graded challenge, but not necessary
- Rate of re-sensitization very low
  - For penicillin, cephalosporin, and beta-lactam
- **Remove the allergy and educate patient**

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Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

Positive Penicillin Skin Test

- 50% or higher incidence of reaction after penicillin administration
- Consider alternative antibiotic and avoid first generation cephalosporins
  - 2nd, 3rd, 4th generation cephalosporins may still be safe
  - Carbapenems and monobactams likely safe
- If no alternative therapy, consider desensitization
  - Induction of drug tolerance appears safe in patients with Type 1 allergy

Clin Rev Allergy Immunol. 2012;43(1-2):84-97.
J Pharm Pract 2014. 27(6):530-44.

Graded Drug Challenge vs. Desensitization

	Graded Drug Challenge	Desensitization
History of allergy	Vague, **unlikely IgE-mediated**	Proven, **clear allergic events** (hives, angioedema, anaphylaxis)
Reason to perform and goal	**Disprove hypersensitivity,** Confirm ability to receive penicillin	No alternative therapies, **Generate temporary tolerance**
Relative contraindications	Concurrent illness Suspect true IgE allergy	Uncontrolled asthma, concurrent illness, hemodynamic instability
Absolute contraindications	**Non IgE-mediated event (SJS, DRESS)**	
Starting dose	1:100 therapeutic dose	**1:1,000,000** or 1:100,000 of therapeutic dose
Steps to complete test	3-5	10-20
Time to complete test	1-3 hours	**2-6 hours**
Location	**Clinic or inpatient**	Inpatient, Emergency Department, ICU
Sustainability	**Once allergy disproven, drug can be given in the future**	Temporary, ongoing administration necessary to maintain tolerance

Clin Rev Allergy Immunol. 2012;43(1-2):84-97.

Suspected Type II-IV Allergy

- No tests exist, cross-reactivity unknown for most
  - Diagnose based on detailed history
  - **Avoid penicillin and all related drugs (including skin testing) if Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN)**
- History of non-pruritic morbilliform eruption
  - Often, not distinguishable from urticaria based on history
  - Can consider graded drug challenge with close monitoring
    - Be mindful of similar side-chain drugs
    - NOT in patients with a history of SJS/TEN

Update the record!

- Allergy history documentation is poor
- Allergy records are rarely updated to demonstrate tolerance
  - In one institution, **only 18%** of patients with a reported penicillin allergy who received a penicillin antibiotic without incident had their records updated
- Algorithms to guide penicillin allergy histories can improve documentation

J Allergy Clin Immunol Pract. 2017 Jan - Feb;5(1):184-186.
Staicu ML. ID Week 2016

A proactive approach to penicillin allergy testing in hospitalized patients

- **Objective:** Evaluate patients with penicillin allergy to remove inaccurate diagnosis and reduce use of beta-lactam alternatives
- **Methods:** Penicillin skin tests and challenges performed by clinical pharmacist
- **Results:** 228 of 252 subjects (90.5%) had penicillin allergy removed
  - 85 (38%) patients received beta-lactams
- **Conclusions:** Penicillin allergy testing effectively removed reported allergies in hospitalized patients

J Allergy Clin Immunol Pract. 2016 Nov 22. Epub ahead of print.

Beta-lactams allergies are the most commonly reported drug allergies

- Several are not truly allergic in nature

There are major public health implications of inadequate allergy documentation

- Often lead to avoidance of preferred therapy
- Poorer outcomes, higher cost, greater toxicity, higher risk of resistance

Cross-reactivity between penicillins and other beta-lactams is lower than originally thought

- Certain cephalosporins, carbapenems, and monobactams present low risk

Accurate and detailed allergy history is crucial for optimal antibiotic therapy

- Penicillin skin testing and graded drug challenges are useful diagnostic measures
- Always update the medical record when information is gained

Conclusions

Beta-lactam Allergies: Misadventures of Misreporting

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